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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,295	09/09/2002	Menachem Rubinstein	RUBINSTEIN=7	2828

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EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,295	RUBINSTEIN ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-11* is/are pending in the application.

4a) Of the above claim(s) *6-8 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/9/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group 9, claim 9 and the species CSC in the reply filed on 12/15/2005 is acknowledged. The traversal is on the ground(s) that groups 7-9 share special technical feature of administering a leptin, a homologue or a derivative and further argues that the amended claim 5 and the new claim11 encompass the same invention. Applicant's arguments are found persuasive and therefore, claims 5, 9, and 11 are examined to the extent they read on the elected species of VEGF inhibitor – CSC.

The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, And/Or Claims

Claims 1-4 are canceled.

Claims 5-11 are pending.

Claims 6-8 and 10 are withdrawn from further consideration as being drawn to a nonelected Invention.

Claims 5, 9 and 11 are examined on the merit to the extent that they read on the elected invention of VEGF inhibitor – CSC.

Claim Objections

Claim 5 is objected for the use of many abbreviated phrases (VEGF, CSC, DMPX, sFLT-1), which should be described for the first time followed by an abbreviated form placed in a bracket. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 9 and 11are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn a method of reversibly inhibiting endothelial proliferation by administering any leptin homologue or derivative. The claims do not require that the leptin homologue or derivative possess any particular conserved structure, or any other disclosed distinguished feature. Thus the claims are drawn to a genus of polypeptides variant or derivative that is defined by a large number of amino acid substitutions, deletions, insertions or chemical modifications.

To provide possession of a claimed invention, the specification must provide sufficient distinguishing identifying characteristics for the invention. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, method of making an invention or any combination thereof. The specification does not provide a definition of " a derivative" or disclose any derivative of leptin or leptin homologue. As such the

genus "leptin derivative or a homologue" encompasses any compound, peptide, protein or agent that can reversibly inhibit endothelial cell proliferation.

This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the Awritten description inquiry, is *whatever is now claimed* (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly & Co., 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus,

the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B (1), the court states an adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of leptin derivative, or homologoue and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making a mutation. The compound itself is required. See Fiers v.Revel, 25USPQ2d 1601 at 1606 (CAFC 1993) and Amgen v.Baird, 30 Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 148 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. Therefore, only the leptin polypeptide, but not the breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 5, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enables for administering leptin with or without CSC in rat, still does not reasonably provide enablement for reversibly inhibiting endothelial cell

proliferation by administering leptin, a homologue or a derivative thereof in any mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to which the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The Nature of the Invention: The claims are drawn to a method for reversibly inhibiting endothelial cell proliferation in any mammal comprising administering leptin, or a homologue or a derivative that reversibly inhibits endothelial cell proliferation.

The state of the prior art and the predictability or lack thereof in the art:

Leptin is a 16 kD protein that is produced by adipocytes and induces weight loss in normal as well as genetically obese ob/ob mice. Leptin promotes wound heeling in a dose dependent manner by interacting with its receptor (Ring et al., Endocrinology 141: 446-449, 2000). Bouloumie et al (Circulation Res 83 : 1059-1066, 1998) teach that leptin induces angiogenesis in human umblical venous endothelial cells (HUVECs) in a dose dependent manner. A number of genes play a role in angiogenesis and endothelial cell proliferation. For example, Teichert-Kuliszewska et al. (Cardiovacular Res. 49: 659-670, 2001) teach the role of angiopoietin-1 (Ang1) and angiopoietin-2 (Ang2) in endothelial cell proliferation. They teach that Ang2 was previously known as an antagonist of Ang1. But further detailed studies suggest that the mechanism of endothelial cell proliferation is a balancing act of combination of Ang1 and Ang2. They teach, on page 660, that animals overexpressing Ang2 show a phenotype similar to Ang1 knockout. Further, Ang1 and Ang2 potentiate the vascular endothelial growth

factor (VEGF) induced angiogenesis in vivo in mouse corneal micropocket assay. They cite several reports to support Ang2 role in angiogenesis. The role of leptin derivatives which encompass compounds, peptides, amino acid deletion or insertions would be unpredictable because it is not defined by any structure, physical and/or chemical properties, functional characteristics, structure/function correlation on how to make a derivative and use it. Combination of VEGF inhibitor with leptin or leptin derivatives to modulate endothelial cell proliferation is unpredictable. This would further depend on VEGF inhibitor's potential to inhibit angiogenesis. Therefore, a large number of experimentation would be required to determine reversible inhibition of endothelial cell proliferation by administering leptin, a homologue or a derivative thereof.

The amount of direction and guidance present and the presence or absence of working examples: Given the teachings of unpredictability found in the art, detailed teachings are required to be present in the disclosure in order to enable the skilled artisan to practice the invention commensurate in scope with the claims. These teachings are absent. The specification (examples 2-3) teaches that leptin induces Ang2 and probably Ang2 is responsible for the inhibition of endothelial cell proliferation. However, reports on Ang2 and leptin as an angiogenesis inhibitor are controversial. The specification does not teach a mammal model which is predictable regarding reversible endothelial cell proliferation. Therefore, it would require a large amount of experimentation for reversibly inhibiting endothelial cell proliferation using leptin, leptin homologue or derivatives in mammals.

The breadth of the claims and the quantity of experimentation needed:

Because the claims encompass a method of reversibly inhibiting endothelial cell proliferation using leptin, homologue or a derivative in combination of a VEGF inhibitor, in the light of the teachings of the unpredictability found in the art discussed and because of the supra lack of sufficient teachings in applicants disclosure to overcome those teachings, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PATENT EXAMINER